

DiPiro's Pharmacotherapy Handbook, 13th Edition >

Chapter 25: Hepatitis, Viral

INTRODUCTION

- Viral hepatitis refers to the clinically important hepatotropic viruses responsible for hepatitis A (HAV), hepatitis B (HBV), delta hepatitis, hepatitis C (HCV), and hepatitis E.

HEPATITIS A

- HAV infection usually produces a self-limited disease and acute viral infection, with a low fatality rate, and confers lifelong immunity. Outbreaks occur each year in the United States.
- HAV infection primarily occurs through transmission by the fecal-oral route, person-to-person, or by ingestion of contaminated food or water. HAV's prevalence is linked to resource-limited regions and specifically to those with poor sanitary conditions and overcrowding. Rates of HAV infection are increased among persons who inject drugs, persons experiencing homelessness, and men who have sex with men.
- The disease exhibits three phases: (1) incubation (averaging 28 days, range 15–50 days), (2) acute hepatitis (generally lasting 2 months), and (3) convalescence. Acute hepatitis is marked by an abrupt onset of nonspecific symptoms, some very mild. Some patients may experience symptoms for up to 9 months. Nearly all individuals have a clinical resolution within 6 months of the infection, and a majority have resolution within 2 months. HAV does not lead to chronic infections.
- The clinical presentation of HAV infection is given in **Table 25-1**. There are no specific symptoms unique to HAV. Children younger than 6 years of age are typically asymptomatic.
- The diagnosis of acute HAV is made through the immunoglobulin M (IgM) anti-HAV, which is detectable 5–10 days prior to symptomatic HAV infections in the majority of patients. Clinical criteria consist of acute onset of fatigue, abdominal pain, loss of appetite, intermittent nausea and vomiting, jaundice or elevated serum aminotransferase levels, and serologic testing for IgM anti-HAV.



TABLE 25-1

Clinical Presentation of Acute Hepatitis

	Hepatitis A (HAV)	Hepatitis B (HBV)	Hepatitis C (HCV)
Signs and symptoms	>70% of patients are symptomatic with fever, jaundice, scleral icterus, hepatomegaly. Less common: splenomegaly, skin rash, arthralgia.	Approximately 70% of patients are anicteric or subclinical. Younger patients are most likely to be asymptomatic. If symptoms occur, jaundice, dark urine, white stool, abdominal pain, fatigue, fever, chills, loss of appetite, and pruritus are possible with acute infection. Chronic infections tend to be asymptomatic.	Approximately 70% of patients are asymptomatic. If symptoms occur, acute infection can cause jaundice, dark urine, white stool, abdominal pain, fatigue, fever, chills, loss of appetite, and pruritus. Chronic infections tend to be asymptomatic.
Laboratory Findings in the Acute Phase of Infection			
Aminotransferase (ALT, AST) elevations	>1000 IU/L (6.7 μ kat/L) ALT>AST	1000–2000 IU/L (16.7–33.3 μ kat/L) ALT>AST	Highly variable, can be approximately 1000 IU/L (16.7 μ kat/L) ALT>AST
Bilirubin	Elevated and preceded by aminotransferase elevations	Can be within normal or elevated	Elevated and preceded by aminotransferase elevations
Virus-specific tests	IgM anti-HAV	IgM anti-HBc (+), HBsAg (+)	HCV RNA (+) or quantifiable; HCV antibody reactive within 12 weeks of exposure
Aminotransferase (ALT, AST) elevations Aminotransferase (ALT, AST) Elevations	NA Acute infection only	ALT > AST Variable, can be within normal limits or elevated	ALT > AST Variable, can be within normal limits or elevated
Bilirubin	NA	Can be normal or elevated	Can be normal or elevated
IgG anti-HAV or total IgG for prior infection or vaccination	HBsAg (+) for active infection	HCV antibody and HCV RNA (+) or quantifiable	

ALT, alanine aminotransferase; anti-, antibody to; AST, aspartate aminotransferase; HBc, hepatitis B core; HBsAg, hepatitis B surface antigen; Ig, immunoglobulin; IU, international units; L, liter; RNA, ribonucleic acid.

PREVENTION

- HAV is easily preventable with vaccination. The spread of HAV can be best controlled by avoiding exposure. The most important measures to avoid exposure include good handwashing techniques and personal hygiene practices.
- The current vaccination strategy in the United States includes vaccinating all children. Groups who should receive HAV vaccine are shown in [Table 25-2](#). Vaccination is also recommended for adults at risk for worse outcomes with HAV infection, including for persons over the age of 40 and persons with immunocompromising conditions, chronic liver disease, and human immunodeficiency virus (HIV).

- Three inactivated virus vaccines are licensed in the United States: Havrix, VAQTA, and Twinrix. Approved dosing recommendations are shown in [Table 25-3](#). Seroconversion rates of 94% or greater are achieved with the first dose.
- Common vaccine side effects include soreness and warmth at the injection site, headache, malaise, and pain.
- Ig (GamaSTAN) is used when pre- or postexposure prophylaxis against HAV infection is needed in persons for whom vaccination is not an option. Dosing of Ig is the same for adults and children. It is most effective if given during the incubation phase of infection. A single dose of Ig 0.02 mL/kg is given intramuscularly for postexposure prophylaxis or short-term (<3 months) preexposure prophylaxis. For lengthy stays (≤5 months), a single dose of 0.06 mL/kg is used. HAV vaccine may also be given with Ig.
- Ig is recommended with vaccination if travel to an HAV high- or intermediate-risk country will begin in <2 weeks and the individual is an older adult, is immunocompromised, or has chronic liver disease or other chronic medical condition.
- Anaphylaxis to Ig has been reported in patients with IgA deficiency.

TABLE 25-2

Recommendations for Hepatitis A Virus Vaccination

All children at 12–23 months
Any unvaccinated children ages 2–18 years
International travelers^a
Men who have sex with men
Users of injection and noninjection drugs
People experiencing homelessness
Persons with occupational risk for infection (eg, persons who work with HAV-infected primates or with HAV in a research laboratory)
Persons with chronic liver disease, including persons with hepatitis B virus infection, hepatitis C virus infection, metabolic-associated liver disease, alcohol-related liver disease, autoimmune hepatitis, or cirrhosis. People with HIV infection
Pregnant women at risk for HAV infection or severe outcomes from HAV infection
All previously unvaccinated persons anticipating close personal contact (eg, household contact or regular babysitter) with an international adoptee from a country of high or intermediate endemicity within the first 60 days after the arrival of the adoptee
Anyone who would like to obtain immunity

HAV, hepatitis A virus; HIV, human immunodeficiency virus.

Data from the Centers for Disease Control and Prevention.

^aTravelers to Canada, Western Europe, Japan, Australia, or New Zealand are at no greater risk for infection than they are in the United States. All other travelers should be assessed for HAV risk.

TABLE 25-3

Recommended Dosing of Hepatitis A Vaccines

Vaccine	Age (Years)	Dose of Hepatitis A Antigen (Volume)	No. of Doses	Schedule ^a
Havrix	1–18	720 ELISA units (0.5 mL)	2	0, 6–12 months
	≥19	1440 ELISA units (1 mL)	2	0, 6–12 months
VAQTA	1–18	25 units (0.5 mL)	2	0, 6–18 months
	≥19	50 units (1 mL)	2	0, 6–18 months
Twinrix ^b	≥18	720 ELISA units (1 mL)	3	0, 1, 6 months
	≥18 (accelerate schedule)	720 ELISA units (1 mL)	4	0, 7 days, 21–30 days, +12 months

ELISA, enzyme-linked immunosorbent assay.

Data from the Centers for Disease Control and Prevention.

^aZero (0) denotes initial dose, subsequent numbers denote time after initial dose for timing of additional doses.

^bCombination of hepatitis A and B vaccines, also contains 20 mcg of hepatitis B surface antigen, and requires a three-dose schedule for adequate HBV response.

TREATMENT

- No specific treatment options exist for HAV. Management of HAV infection is primarily supportive. Corticosteroid use is not recommended.

HEPATITIS B

- HBV is a leading cause of chronic hepatitis, cirrhosis, and hepatocellular carcinoma (HCC).
- Transmission of HBV occurs sexually, parenterally, and perinatally. In areas of high HBV prevalence, perinatal transmission from mother to child at birth is the most common. In the United States, injection drug use and sexual contact continue to be key routes of transmission, although a large percentage of patients with acute HBV had no identified risk factor.
- A triple panel is used to diagnose HBV with hepatitis B surface antigen (HBsAg), antibody to hepatitis B core (anti-HBc), and antibody to hepatitis B surface (anti-HBs). HBsAg is detectable at the onset of clinical symptoms. Its persistence past 6 months after initial detection corresponds to chronic infection and indicates an increased risk for cirrhosis, hepatic decompensation, and HCC.
- The interpretation of serologic markers for HBV is given in [Table 25-4](#).
- The clinical presentation of HBV infection is given in [Table 25-1](#).

TABLE 25-4

Interpretation of Serologic Tests in Hepatitis B Virus

Tests	Result	Interpretation
HBsAg Anti-HBc Anti-HBs	(-) (-) (-)	Susceptible: offer vaccine
HBsAg Anti-HBc Anti-HBs	(-) (+) (+)	Past HBV infection, resolved No further management is needed unless undergoing immunosuppressive therapy or chemotherapy
HBsAg Anti-HBc Anti-HBs	(-) (-) (+)	Immune because of vaccination (valid only if test performed 1–2 months after third vaccine dose)
HBsAg Anti-HBc IgM anti-HBc Anti-HBs	(+) (+) (+) (-)	Acute infection
HBsAg Anti-HBc IgM anti-HBc Anti-HBs	(+) (+) (-) (-)	Chronic infection. Link to care and further evaluation
HBsAg Anti-HBc Anti-HBs	(-) (+) (-)	Possible interpretations: Resolved infection or false positive. If patient is immunocompromised, check HBV DNA

Anti-, antibody to; HBc, hepatitis B core; HBsAg, hepatitis B surface antigen; HBs, hepatitis B surface; IgM, immunoglobulin M.

Note: Anti-HBc includes both IgM anti-HBc and IgG anti-HBc. IgM is present during acute phase of infection.

Data from Hepatitis B Serology, Centers for Disease Control and Prevention. <https://www.cdc.gov/hepatitis/hbv/interpretationofhepbserologicresults.htm>.

PREVENTION

- Prophylaxis of HBV can be achieved by vaccination (HBV vaccine) or by passive immunity in postexposure cases with HBV Ig, which provides temporary passive immunity.
- The goal of immunization against viral hepatitis is prevention of the short-term viremia that can lead to transmission of infection, clinical disease, and chronic HBV infection.
- Vaccination is the most effective strategy to prevent HBV infection. Persons who should receive HBV vaccine are listed in **Table 25-5** and vaccine dosing is in **Table 25-6**.
- The most commonly reported adverse events are nausea/dizziness and fever/headache for single-antigen vaccines and fever, injection site erythema, and vomiting for combination vaccines. For Heplisav-B, the most common adverse reactions reported within 7 days of vaccination

included injection site pain, fatigue, and headache.

TABLE 25-5

Risk Factor–Based Vaccine Recommendations for Adults 60 and Older

- Sex partners of persons who are HBsAg-positive
- Sexually active persons not in a long-term monogamous relationship (>1 partner/6 months)
- Men who have sex with men
- Persons seeking evaluation or treatment for sexually transmitted infection
- Persons with HIV
- Current or recent injection drug use
- Household contacts of persons with chronic hepatitis B infection; clients and staff of institutions for the developmentally disabled
- Healthcare and public safety workers with anticipated risk for exposure to blood or blood-contaminated fluid in the workplace
- Patients with ESRD or on chronic dialysis, including predialysis, peritoneal dialysis, and home dialysis
- Incarcerated persons
- International travelers to regions with high or intermediate levels (HBsAg prevalence >2%) of endemic HBV infection
- Persons with chronic HCV infection
- Persons with chronic liver disease (eg, patients with alcohol-induced liver disease, cirrhosis, fatty liver disease, autoimmune hepatitis)
- All unvaccinated adults seeking vaccination (specific risk factor not required)

ESRD, end-stage renal disease; HIV, human immunodeficiency virus.

TABLE 25-6

Recommended Dosing of Hepatitis B Vaccines (HBV Antigen Vaccines)

Vaccine	Age (Years)	Dose (Volume)	No. of Doses	Schedule ^a
Engerix-B	0–19	10 mcg IM (0.5 mL)	3	0, 1, 6 months
	>20	20 mcg IM (1 mL)	3	0, 1, 6 months
Recombivax	1–19	10 mcg IM (0.5 mL)	3	0, 1, 6 months
	>20	10 mcg IM (1 mL)	3	0, 1, 6 months
Heplisav-B ^{b,c}	≥18	0.5 mL	2	0, 1 months
PreHevbrio ^c	≥18	1 mL	3	0, 1, 6 months

IM, intramuscularly.

^aZero (0) denotes the initial dose; subsequent numbers denote the time after the initial dose for the timing of additional doses.

^bUtilizes different adjuvant; cannot be interchanged with other HBV vaccines.

^cCannot be interchanged with other HBV vaccines.

TREATMENT

- **Goals of treatment:** The goals of therapy are to suppress HBV replication and prevent disease progression to cirrhosis and HCC. Other important goals are preventing mother-to-child transmission and reactivation in patients with inactive HBV infections.
- Some patients with chronic HBV infection should be treated. Recommendations for treatment consider the patient's age, serum HBV DNA and alanine aminotransferase (ALT) levels, and whether or not the patient has cirrhosis. All patients with cirrhosis require HBV treatment, irrespective of DNA or ALT levels. Persons without cirrhosis who have low levels of HBV DNA (<2000 IU/mL [kIU/L]) may be managed by periodic monitoring. Generally accepted criteria for treatment of HBV are given in **Table 25-7**.
- All patients with chronic HBV infection should be counseled on preventing disease transmission, avoiding **alcohol**, and being immunized against HAV. Sexual and household contacts should be vaccinated against HBV.
- The preferred nucleos(t)ide analogs for treatment are **entecavir**, **tenofovir disoproxil**, and **tenofovir alafenamide**.
- The immune-mediating agents approved for HBV treatment are interferon (IFN)-**alfa** and **pegylated IFN-alfa**. IFN is not recommended as a first-line therapy.
- Most children with chronic HBV are asymptomatic and do not meet the established criteria for HBV treatment. Treatment is recommended in HBeAg-positive children aged 2–18 who have elevated ALT and measurable HBV DNA.
- To prevent mother-to-child transmission, all infants born to HBsAg-positive women should receive HBV vaccination and Ig within 12 hours of birth.

TABLE 25-7

Generally Accepted Criteria for Treatment of HBV

Characteristics

Anyone with HBeAg (+) or HBeAg (–) active HBV defined as:

HBV DNA >2000 IU/mL (kIU/L)

ALT 2 × upper limit of normal^a and/or with evidence of histological disease^b

Anyone with compensated or decompensated cirrhosis with HBV DNA >2000 IU/mL (kIU/L)^c

Anyone not fulfilling the above criteria with ALT <2 × ULN and any detectable HBV DNA (<2000 IU/mL [kIU/L]), consider:

Patient's age (especially >40 years)

Family history of HCC or cirrhosis

Prior history of HBV treatment

Extrahepatic manifestations of HBV

HBeAg, hepatitis B e-antigen.

^aPer European guidelines, any elevations in ALT.

^bModerate or greater fibrosis as determined by biopsy or noninvasive measures.

^cPer European guidelines, any detectable HBV DNA.

HEPATITIS C

- HCV infection is prevalent in high-risk populations such as persons who inject drugs. Less common routes of transmission include sexual transmission and infants born to HCV-infected women. Universal HCV screening is recommended for all persons aged 18 and older (**Table 25-8**).

- The initial test for HCV infection is the anti-HCV or antibody test. Patients who are antibody positive for HCV require confirmatory testing for HCV RNA to verify current HCV infection.
- In an acute HCV infection, most patients are asymptomatic and undiagnosed. HCV RNA is detectable within 1–2 weeks of exposure and levels rise quickly during the initial weeks.
- One-third of adults will experience some mild and nonspecific symptoms, including fatigue, anorexia, weakness, jaundice, abdominal pain, or dark urine.
- Up to 85% of acutely infected patients go on to develop chronic HCV infection, defined as persistently detectable HCV RNA for 6 months or more. Most patients will have few, if any, specific symptoms of chronic HCV infection.
- HCV cirrhosis poses a 30% risk of developing the end-stage liver disease over 10 years as well as a 1%–2% risk per year of developing HCC.

TABLE 25-8

Recommendations for Hepatitis C Virus Screening

- All adults ≥18 years
All pregnant females during each pregnancy
Routine periodic testing for persons with ongoing risk factors:
- Persons who inject drugs, share needles, syringes, or other drug preparation equipment
 - Persons undergoing maintenance hemodialysis
 - Sexually active MSM with HIV
 - MSM at initiation of HIV pre-exposure prophylaxis

HIV, human immunodeficiency virus, MSM, men who have sex with men.

TREATMENT

- **Goals of treatment:** The goal is to eradicate HCV infection, which prevents the development of chronic HCV infection, end-stage liver disease, HCC, and death.
- Virologic cure, or sustained virologic response (SVR), is defined as a nondetectable HCV RNA at least 12 weeks after completing HCV therapy. Patients who achieve SVR will continue to have detectable HCV antibody, although this does not imply HCV immunity.
- Treatment is recommended for all HCV-infected persons. Patients with a short life expectancy are the only populations for whom treatment is not recommended.
- Patients without cirrhosis may be candidates for a much more simplified treatment approach if the patient is HCV treatment naïve, has no history or suspicion of HCC, has not received a liver transplant, and has no evidence of HIV or active HBV infection. Patients with cirrhosis must be further evaluated to determine if the cirrhosis is compensated (Child-Pugh score [CTP] A) or decompensated (CTP B or C). Patients with decompensated cirrhosis should be treated by clinicians with expertise in managing advanced liver disease.
- The following laboratory tests are suggested prior to treatment: HCV RNA, complete blood count, liver function tests, international normalized ratio, glomerular filtration rate, HIV antigen/antibody, hepatitis B serologies, and anti-HAV. On-treatment laboratory monitoring is not necessary for patients without cirrhosis who meet the criteria for the simplified algorithm.
- The simplified treatment regimen for treatment-naïve patients with hepatitis C (all genotypes) is **glecaprevir/pibrentasvir** three tablets orally daily with food × 8 weeks, or **sofosbuvir/velpatasvir** one tablet orally daily with or without food × 12 weeks. HCV RNA and liver function tests should be repeated 12 weeks after completing HCV therapy to assess for cure (SVR) and resolution of hepatic inflammation.

- Patients without cirrhosis and those with compensated cirrhosis are treated similarly with no difference in treatment duration.
- Patients with decompensated cirrhosis often require concomitant **ribavirin** and have fewer treatment options due to the underlying level of liver disease and concerns for safety.
- Clinically significant drug–drug interactions are expected with **carbamazepine**, **phenobarbital**, **phenytoin**, **oxcarbazepine**, **rifampin**, and St. John’s wort, and concurrent use of these agents with any of the HCV therapies is expected to result in HCV treatment failure.
- All patients with chronic HCV infection should be vaccinated for HAV and HBV (**Table 25-9**).

TABLE 25-9

AASLD/IDSA Recommended HCV Treatment Regimens for Treatment-Naïve Patients Without Cirrhosis (All Genotypes)

Simplified Treatment Algorithm		
Glecaprevir/pibrentasvir 3 tabs orally daily with food × 8 weeks	Or	Sofosbuvir/velpatasvir 1 tab orally daily with or without food × 12 weeks
Repeat HCV RNA and LFTs 12 weeks after completing HCV therapy to assess for cure (SVR) and resolution of hepatic inflammation		

AASLD, American Association for the Study of Liver Diseases; IDSA, Infectious Diseases Society of America; LFTs, liver function tests; SVR, sustained virologic response.

See **Chapter 61**, *Viral Hepatitis*, authored by *Paulina Deming*, for a more detailed discussion of this topic.